Some clinical, epidemiological and histopathological data support the occurrence of a specific cardiomyopathy related to diabetes mellitus, independent of hypertension and coronary artery disease. The pathogenesis of diabetic cardiomyopathy is partially understood and is likely to be multifactorial, involving metabolic disturbances and autonomic neuropathy. This review discusses the possible mechanisms that may be involved in the development and progression of cardiac dysfunction in diabetes, and seeks to define the best approach to prevent and reduce the cardiovascular morbidity and mortality of diabetic cardiomyopathy.

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Key words: Diabetic Cardiomyopathy; Diabetes Mellitus; Ambulatory Blood Pressure Measurement; Diabetic Autonomic Neuropathy

## INTRODUCTION

Some clinical, epidemiological and histopathological data support the occurrence of a specific cardiomyopathy related to diabetes mellitus (DM). However, the exact etiology of this complication remains uncertain[1-4]. Diabetes mellitus has multifactorial detrimental effects on myocardial tissue[5] and is commonly associated with hypertension and coronary atherosclerosis[6], which can singly reduce myocardial performance and increase cardiovascular mortality. Therefore, considering the numerous confounders, especially in type 2 diabetes, it is difficult to determine whether diabetic cardiomyopathy is a unique clinical entity independent of other conditions, due exclusively to the direct effects of the abnormal myocardial metabolism in diabetes.

The existence of diabetic cardiomyopathy was first suggested by Rubler et al in 1972, on the basis of autopsy findings in four diabetic adults with congestive heart failure in the absence of coronary, valvular, congenital and hypertensive heart disease[7]. The role of DM as a causal factor in the development of congestive heart failure was more conclusively delineated in the Framingham Heart Study, which found this condition to be more frequent in diabetic patients when compared to age-matched control subjects, independently of age, weight, office blood pressure, hypercholesterolemia and coronary artery disease[8]. Studies using independent population databases have provided similar results, revealing increased heart failure rates in subjects with diabetes mellitus in cross-sectional analyses and increased risk for developing heart failure in prospective analyses, even after correction for confounding variables[9-11].

The pathogenesis of diabetic cardiomyopathy is partially understood and is likely to be multifactorial, involving complex cellular and molecular perturbations that predispose to altered myocardial structure and function. Some appealing hypotheses to explain the development of this condition have been proposed, and include metabolic disturbances (hyperglycemia, hyperinsulinemia and abnormalities in myocardial lipid metabolism) and autonomic neuropathy (AN)[1,12-14].
CARDIAC PRECLINICAL DAMAGE

Diabetic cardiomyopathy is a distinct entity diagnosed when ventricular dysfunction develops in patients with diabetes in the absence of coronary atherosclerosis and hypertension. The most commonly observed cardiac abnormalities in clinical studies of asymptomatic diabetics include diastolic cardiac dysfunction and left ventricular hypertrophy, which configure preclinical abnormalities.

In regard to the clinical evaluation of the preclinical abnormalities of diabetic cardiomyopathy, it is noteworthy that the diastolic function parameters (peak flow velocity of early left ventricular filling, peak flow velocity of late left ventricular filling, early deceleration time, isovolumetric relaxation period and the ratio between early and late diastolic flow velocity peaks) are useful in population studies, but present significant individual variability. Additionally, despite the excellent reliability of echocardiography for measurement of left ventricular mass (intraclass coefficient of correlation 0.86), the 95% confidence interval (CI) width of a single replicate measurement of left ventricular mass is 59 grams, exceeding usual decreases in mass during treatment. However, within a population, the CI decreases proportionally with the inverse of the square root of the sample size, which makes it possible to evaluate decreases and increases in LVMI in large groups.

Left ventricular diastolic dysfunction has been widely reported in diabetic animals and diabetic patients without evidence of heart disease caused by other factors. Studies of well-controlled type 2 diabetic subjects without clinically detectable heart disease showed that 52 to 60% of them had diastolic dysfunction. Abnormal diastolic inflow patterns reflect underlying disorders in relaxation and/or reduced myocardial compliance, associated with myocardial fibrosis. Echocardiographic changes consistent with left ventricular hypertrophy (LVH) have been described in a number of studies of diabetic populations and may portend an increased risk for the subsequent development of heart failure, particularly in the presence of coexisting hypertension. In the Framingham Heart study, diabetic women had a left ventricular mass index (LVMI) 10% greater than the nondiabetic patients.

Additionally, left ventricular hypertrophy and cardiac diastolic dysfunction are more frequent and more likely to become clinically apparent in diabetic patients when associated with hypertension, suggesting a maximization of damage on the myocardium in the presence of both DM and hypertension. The reduction of 10% in LVMI was associated with a fasting blood glucose reduction from 178±36 to 147±30 mg/dL (p<0.01) and a correlation was observed between blood glucose and LVMI percent variations (r=0.5, p<0.01). These results occurred independently of blood pressure and cholesterol levels, in diabetics without coronary artery disease. However, we didn’t perform ABPM in these patients. The better glycemic control could be responsible for a reduction of nocturnal blood pressure levels, which could explain the improvement of the left ventricular mass index. Thus, the glycemic control would have an indirect effect on the left ventricular hypertrophy.

Furthermore, we found that diabetics with nocturnal systolic blood pressure greater than 140 mmHg and elevated fasting blood glucose levels showed an additional risk of LVH (p<0.05; odds ratio=11) (Figure 1).

A few short-term studies have shown that systolic left ventricular pressure may improve if hyperglycemia is corrected. However, the abnormalities in diastolic cardiac function are considered to be largely irreversible. Accordingly, in our study, there were no important changes in left ventricular diastolic function when glycemic control was improved.

Other authors argue that hyperglycemia could be one of the main responsible for the damage caused by diabetes on the myocardium. Barbagallo et al. performed a multivariate regression, which indicated that the contribution of glucose levels to LVMI was independent of age, body mass index, fasting insulin levels and blood pressure, and demonstrated a significant interaction with intracellular calcium (Cai). Altogether, these data suggest that preclinical alteration, potentially related to subsequent development of diabetic cardiomyopathy.

ROLE OF HYPERGLYCEMIA

The severity and duration of hyperglycemia has been shown to directly parallel the incidence of diabetic cardiomyopathy in patients with diabetes. We were the first ones to demonstrate, in 2000, that the improvement of glycemic control in type 2 diabetic patients per se is capable of reverting left ventricular hypertrophy. The reduction of 10% in LVMI was associated with a fasting blood glucose reduction from 178±36 to 147±30 mg/dL (p<0.01) and a correlation was observed between blood glucose and LVMI percent variations (r=0.5, p<0.01). These results occurred independently of blood pressure and cholesterol levels, in diabetics without coronary artery disease. However, we didn’t perform ABPM in these patients. The better glycemic control could be responsible for a reduction of nocturnal blood pressure levels, which could explain the improvement of the left ventricular mass index. Thus, the glycemic control would have an indirect effect on the left ventricular hypertrophy.

Figure 1 Risk of left ventricular hypertrophy and average of fasting blood glucose values in patients with nocturnal systolic blood pressure greater than 140 mmHg. LVMI=left ventricular mass index; AFBG=average of fasting blood glucose; LVH=left ventricular hypertrophy.
Diabetic autonomic neuropathy, characterized by denervation and alterations in myocardial catecholamine levels, has been associated with a high cardiac mortality rate. Cardiovascular autonomic neuropathy (CAN) is an independent risk factor for cardiovascular mortality and silent myocardial infarction. Histological evidence of AN has been found in diabetic patients with painless myocardial infarction and autopsy studies have found low concentrations of noradrenaline in diabetic patients. Kahn et al., comparing diabetics with and without AN, found that the former had reduced levels of plasma catecholamines and that this finding was related to abnormalities in diastolic cardiac function. Sympathetic stimulation not only increases the contractility of the left ventricle but also increases their rate of relaxation.

In early stages, CAN may be completely asymptomatic and detected by changes in heart rate variability and abnormal cardiovascular reflex tests (R-R response to deep breathing, standing and Valsalva maneuver). Advanced disease may be indicated by resting tachycardia (>100 bpm) and orthostasis (a fall in systolic blood pressure >20 mmHg or diastolic blood pressure of at least 10 mmHg upon standing without an appropriate heart rate response). The standard cardiovascular reflex testing, especially the deep breathing test, is noninvasive, easy to perform, reliable, reproducible and has prognostic value.

The main determinant of the blood pressure circadian pattern appears to be the sympathetic nervous system and DM has been associated with elevated levels of nocturnal blood pressure. It has been suggested that poor metabolic control could be the mechanism responsible for this elevation. Increased nocturnal blood pressure has been described in diabetic autonomic neuropathy, diabetic nephropathy, essential hypertensive patients with chronic renal failure, malignant hypertension and essential hypertensive patients without other associated pathology. AN could reduce nocturnal decline of blood pressure by reducing vagal tone and a consequent increase in cardiac output during sleep, which has been associated with a higher risk of cardiovascular complications. Ambulatory blood pressure monitoring can be particularly useful in detecting absence or reduction of blood pressure descent during sleep. We assessed the reproducibility of ABPM measurements and the placebo effect on ABPM to determine its degree of reliability as to the measurement of pressure levels in patients with type 2 DM and hypertension. The results of our study showed that mean pressure values assessed by ambulatory blood pressure monitoring presented good reproducibility and were not affected by placebo (Figure 2). These findings are similar to few data found in the literature.

We have also demonstrated a correlation of AN tests with LVMI and cardiac diastolic function (CDF) in normotensive patients with DM2. Positive AN tests occurred even before LVH, impaired CDF and diabetic AN symptoms were present. This correlation was not found in the control group. Additionally, in diabetic individuals, AN tests were correlated with average glycated hemoglobin. Our data suggested that AN could precede LVH and be a contributing factor to preclinical cardiac abnormalities in normotensive patients with DM2. Thus, we recommend that AN tests should be regularly performed in patients with DM2, and that any abnormalities in those tests should be followed by a detailed cardiac evaluation.

Additionally, we have found that hypertensive patients with type 2 DM when compared to patients with essential hypertension presented higher nocturnal systolic blood pressure (NSBP), higher LVMI and worse CDF. These findings occurred independently of sex, age, body mass index and diurnal blood pressure levels.

These data reinforce the hypothesis that AN could be a via through which hyperglycemia could increase nocturnal blood pressure and lead to diabetic cardiomyopathy.

Furthermore, we have also demonstrated that the absence or reduction of blood pressure descent during sleep is also associated with other microvascular complications in patients with type 2 DM, such as diabetic retinopathy and nephropathy. Our study showed that diabetic patients with retinopathy had higher NSBP levels than patients with DM2, and that any abnormalities in those tests should be followed by a detailed cardiac evaluation.

Figure 2 Coefficients of variation of pressure measurements determined by ABPM. DSBP=Systolic BP during alertness; DDBP=Diastolic BP during alertness; NSBP=Systolic BP during sleep; NDBP=Diastolic BP during sleep; 24hSBP=24-hour systolic BP; 24hDBP=24-hour diastolic BP.

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<td>Coefficients of variation (%)</td>
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diabetic patients without retinopathy, independent of diurnal blood pressure, age, sex, duration of DM and body mass index. This result was confirmed by multivariate regression analysis, in which NSBP was an independent predictor of diabetic retinopathy. In regard to diabetic nephropathy, we demonstrated in a prospective study that an elevation of nocturnal systolic blood pressure and a loss of nocturnal blood pressure fall might precede the onset of abnormal albuminuria and cardiovascular events in hypertensive normoalbuminuric patients with type 2 diabetes.

**CONCLUSION**

Since diabetic cardiomyopathy is known to have a high prevalence in the asymptomatic type 2 diabetic patient, screening for its presence at the earliest stage of development would be appropriate in order to prevent the progression to congestive heart failure.

Therefore, we suggest that all type 2 diabetic patients should be evaluated by ABPM and echocardiography to identify loss of nocturnal blood pressure fall and preclinical cardiac abnormalities (cardiac diastolic dysfunction and LVH), respectively. Once identified these conditions, an intensive control of 24-hour blood pressure (especially during the night) and hyperglycemia must be achieved. This approach could have a significant impact in the prevention of diabetic cardiomyopathy and reduce cardiovascular morbidity and mortality in these patients.

**CONFLICT OF INTERESTS**

There are no conflicts of interest with regard to the present study.

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**Peer reviewers:** Jun LU, Faculty of Health & Environmental Sciences, Auckland University of Technology, Private Bag 92006, Box A-25, Auckland 1142, New Zealand; Juei-Tang Cheng, PhD, FCP, Graduate School of Medical Sciences, Chang Jung Christian University, Quei-Ren, Tainan City, Taiwan.